Original Investigation

Pulmonary ^{3}He Magnetic Resonance Imaging Biomarkers of Regional Airspace Enlargement in Alpha-1 Antitrypsin Deficiency

Eric Lessard, BSc, Heather M. Young, BSc, Anurag Bhalla, MD, Damien Pike, PhD, Khadija Sheikh, PhD, David G. McCormack, MD, FRCPC[1], Alexei Ouriadov, PhD, Grace Parraga, PhD

Rationale and Objectives: Thoracic x-ray computed tomography (CT) and hyperpolarized ^{3}He magnetic resonance imaging (MRI) provide quantitative measurements of airspace enlargement in patients with emphysema. For patients with panlobular emphysema due to alpha-1 antitrypsin deficiency (AATD), sensitive biomarkers of disease progression and response to therapy have been difficult to develop and exploit, especially those biomarkers that correlate with outcomes like quality of life. Here, our objective was to generate and compare CT and diffusion-weighted inhaled-gas MRI measurements of emphysema including apparent diffusion coefficient (ADC) and MRI-derived mean linear intercept (L_m) in patients with AATD, chronic obstructive pulmonary disease (COPD) ex-smokers, and elderly never-smokers.

Materials and Methods: We enrolled patients with AATD ($n = 8$; 57 ± 7 years), ex-smokers with COPD ($n = 8$; 77 ± 6 years), and a control group of never-smokers ($n = 5$; 64 ± 2 years) who underwent thoracic CT, MRI, spirometry, plethysmography, the St. George's Respiratory Questionnaire, and the 6-minute walk test during a single 2-hour visit. MRI-derived ADC, L_m, surface-to-volume ratio, and ventilation defect percent were generated for the apical, basal, and whole lung as was CT lung area ≤–950 Hounsfield units (RA_{950}), low attenuating clusters, and airway count.

Results: In patients with AATD, there was a significantly different MRI-derived ADC ($P = .03$), L_m ($P < .0001$), and surface-to-volume ratio ($P < .0001$), but not diffusing capacity of carbon monoxide, residual volume or total lung capacity, or CT RA_{950} ($P > .05$) compared to COPD ex-smokers with a significantly different St. George's Respiratory Questionnaire.

Conclusions: In this proof-of-concept demonstration, we evaluated CT and MRI lung emphysema measurements and observed significantly worse MRI biomarkers of emphysema in patients with AATD compared to patients with COPD, although CT RA_{950} and diffusing capacity of carbon monoxide were not significantly different, underscoring the sensitivity of MRI measurements of AATD emphysema.

Key Words: Alpha-1 antitrypsin deficiency; emphysema; augmentation therapy; hyperpolarized ^{3}He magnetic resonance imaging.

INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD), first described by Laurell and Eriksson in 1963 (1), is an autosomal codominant hereditary disorder caused by a mutation in the SERPINA1 gene, which leads to dysregulation of neutrophil elastase (2). This commonly manifests as early-onset panlobular emphysema and affects approximately 1 in 5000 North Americans (2,3). Respiratory failure accounts for 45%–72% of deaths in patients with AATD. Importantly, an increased risk of mortality may be predicted using computed tomography (CT) biomarkers of emphysema (2) and, overall, outcomes are worse when patients cannot access augmentation therapy (4).

As is the case for smoking-related emphysema, there is no cure for AATD, although current AATD treatments aimed at slowing disease progression include exogenous alpha-1 antitrypsin augmentation therapy. X-ray CT lung density measurements showed that augmentation therapy may slow the rate of emphysema progression in patients with AATD (4)—an important finding that may help guide treatment decisions given the high cost of intravenous augmentation treatment (2). However, although the CT measurement of emphysema

Acad Radiol 2017; ■:■■–■■

From the Robarts Research Institute, 1151 Richmond Street North, London, ON, Canada N6A 5B7 (E.L., H.M.Y., A.B., D.P., K.S., A.O., G.P.); Department of Medical Biophysics, The University of Western Ontario, 1151 Richmond St North, London, ON, Canada N6A 5C1 (E.L., H.M.Y., D.P., K.S., A.O., G.P.); Division of Respirology, Department of Medicine, The University of Western Ontario, London, Ontario, Canada (D.G.MC.). Received March 20, 2017; revised May 2, 2017; accepted May 3, 2017. [1]Present address: London Health Sciences Centre, Victoria Hospital, 800 Commissioners Road East, London, ON, Canada N6G 3G4. **Address correspondence to:** G.P. e-mail: gparraga@robarts.ca

http://dx.doi.org/10.1016/j.acra.2017.05.008

progression was significantly lower in the treatment arm of the Randomized, Placebo-controlled Trial of Augmentation Therapy in Alpha-1 Proteinase Inhibitor Deficiency (RAPID) study, this did not correlate with similar changes in patient-related quality of life measurements (4). This important limitation is also motivating the development of novel biomarkers and intermediate end points of AATD emphysema for novel treatments including gene therapy (5) and pluripotent stem cells (6,7).

The decline over time of the forced expiratory volume in 1 second (FEV_1) (8–10) and the diffusing capacity of carbon monoxide (DL_{CO}) are both considered as biomarkers of AATD lung disease. Although highly variable (11), DL_{CO} measurements correlate with pathology measurements (12) and CT emphysema findings (13) such as the relative area of the CT density histogram ≤–950 Hounsfield units (RA_{950}) (14). More recently, pulmonary imaging biomarkers that exploit the diffusive motion of inhaled polarized gases such as ^{3}He (15) and ^{129}Xe (16) have been measured in patients with emphysema (17) using diffusion-weighted magnetic resonance imaging (MRI) pulse sequences.

In particular, the ^{3}He MRI apparent diffusion coefficient (ADC) was shown to reflect emphysema (15,18). Multiple b-value diffusion-weighted lung MRI (17) also provides estimates of airway space geometry (17,19), based on the heterogeneous gas displacement in the terminal airways that are assumed to be cylindrical in shape (20). Such noninvasive MRI morphometry estimates (17) provide a way to bypass or obviate the necessity for pathological analyses (21–24) and may offer crucial information about lung disease progression, as well as treatment response. Previous MRI studies in patients with AATD (25–28) showed there was no statistical difference in ADC values after 2 years of follow-up (26), but unfortunately, no morphometry data were acquired. MRI morphometry modeling approaches were recently evaluated in patients with chronic obstructive pulmonary disease (COPD) and AATD (29), but this work did not evaluate clinical and other regional biomarkers. This is important because for patients with AATD, emphysematous tissue destruction ensues early in life, and panlobular emphysema is often severe by middle age.

Therefore, the aim of this study was to evaluate patients with AATD using multiple b-value diffusion-weighted MRI as well as pulmonary function and CT measurements of emphysema. We hypothesized that MRI measurements would be highly sensitive to airspace enlargement, which would be significantly worse in patients with AATD as compared to clinically similar ex-smokers with COPD.

MATERIALS AND METHODS

Study Volunteers and Design

All participants provided written informed consent to a study protocol approved by a local research ethics board and Health Canada. Patients aged 40–90 years of age with a diagnosis of AATD and ex-smokers with COPD, >10 pack-years smoking history, and CT evidence of emphysema were recruited from a tertiary care center and evaluated using spirometry, plethysmography, thoracic imaging, the St. George's Respiratory Questionnaire (SGRQ), and 6-minute walk test (6MWT) during a single 2-hour visit. CT evidence of emphysema was defined as an RA_{950} ≥6.8% as previously described (30). We also enrolled older never-smokers (NS) aged 60–80 years, with <0.5 pack-years, and no history of chronic lung disease or uncontrolled cardiovascular disease and completed all study measurements except for the SGRQ and 6MWT.

Spirometry, Plethysmography, SGRQ, and 6MWT

Spirometry measurements were acquired according to the American Thoracic Society guidelines (31) using a whole-body system (MedGraphics Corporation, St Paul, MN). Body plethysmography was also performed for the measurement of lung volumes and DL_{CO} was measured using the attached gas analyzer. The SGRQ (32) was used to establish overall quality of life, and the 6MWT (33) was used to measure exercise capacity.

Image Acquisition

MRI was performed on a whole-body 3T system (MR750 Discovery, GEHC, Milwaukee, WI) with broadband imaging capability (34). ^{3}He MRI employed a whole-body gradient set with maximum gradient amplitude of 50 mT/m and a single-channel, rigid elliptical transmit-receive chest coil (RAPID Biomedical GmbH, Wuerzburg, Germany). The basis frequency of the coil was 97.3 MHz and excitation power was 3 kW using an AMT 3T90 RF power amplifier (GEHC). Subjects were positioned supine in the scanner for both ^{1}H and ^{3}He MRI and instructed by a pulmonary function technologist to inhale a 1-L gas mixture of ^{3}He/N_2 (20% ^{3}He by volume) from functional residual capacity (FRC), with image acquisition performed under breath-hold conditions as previously described (34). ^{3}He gas was polarized to 30%–40% polarization using a spin-exchange optical polarizer (Polarean Inc, Durham, NC). Diffusion-weighted ^{3}He MRI data were acquired using a multi-slice interleaved 2-dimensional gradient echo diffusion-weighted sequence with a matrix size of 128 × 80, for seven 30-mm coronal slices (900 μs selective radio frequency pulse, flip angle $\theta = 4°$, echo time = 3.9 ms, repetition time = 5.6 ms, bandwidth = 62.5 kHz, in-plane resolution = 3.125 × 3.125 mm^2, b = 0, 1.6, 3.2, 4.8, 6.4 s/cm^2); the diffusion-sensitization gradient pulse ramp up-down time was 500 μs with a diffusion time of 1460 μs. The potential for image artifacts associated with radio frequency pulse "history" (35) was addressed by using an optimal constant flip angle (4 degrees) (36). A diffusion-sensitizing, gradient-step, k-space acquisition scheme starting at the maximum b-value was used to ensure that maximum MR signal was acquired for diffusion-weighted images at greater *b*-values. All five *b*-value images were acquired during a single 15-second breath-hold.

Thoracic CT was acquired on a 64-slice Lightspeed VCT scanner (General Electric Healthcare, Milwaukee, WI)